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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,372	11/02/2001	Sojiro Shiokawa	Q64460	8305

7590 08/04/2003

Sughrue Mion Zinn Macpeak & Seas
2100 Pennsylvania Avenue N W Suite 800
Washington, DC 20037-3213

EXAMINER
COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,372	SHIOKAWA ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1,5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-17 are pending in the application.

Priority

1. Any non-provisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross - references to other related applications may be made when appropriate.

"This application is a national stage entry under 35 U.S.C. § 371 of PCT/JP99/06491, filed November 19, 1999." is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of composition and method of use claims are not adequately enabled solely based on serotonin inhibition provided in the

specification. Claims 16 and 17 are the method of use of the compounds of the instant invention for use in the treatment or prevention of any and all diseases and/or disorders associated with serotonin, which is not remotely enabled. The scope of claims 16 and 17 include diseases and/or disorders not even known at this time, which may be associated with serotonin receptors. While the treatment of depression, anxiety, schizophrenia and sleep disorders have been linked with serotonin inhibition, the art does not recognize use of such inhibitors as broad based drugs for treating all disorders instantly embraced. Additionally, instant claim language of claims 12 and 15 embraces disorders not only for treatment but for prevention which is not remotely enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-8 and 11-17 recite a compound represented by the following general formula (1). A formula is not general when all of the variables are defined. Deletion of "general" is suggested.

b) Claim 9 is vague and indefinite in that it is not known what is meant by the colon which follows the last species.

c) Claim 10 is vague and indefinite in that it is not stated in the form of a proper Markush grouping.

d) Claims 11-13 are vague and indefinite in that the terminology "a medicament" does not clarify whether the claim is limited to a compound, composition, or even complex composition.

e) Claims 12 and 13 (and claims dependent thereon) are substantial duplicates of claim 11, as the only difference is a statement of intended use which is not given material weight. Note In re Tuominen 213 USPQ 89.

f) Claim 14 provide for the use of the compounds of formula (1), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

g) Claims 16 and 17 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by serotonin inhibition. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim.

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person

in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound

result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in antidepressants, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over SATO et al., Journal of Medicinal Chemistry. The prior art generically teaches compounds that are structural homologs of the instantly claimed compounds as claimed herein, i.e., they differ by a methyl group. The instant compounds are structural homologs of the reference compounds where on the instant compounds the substituent at the 4-position of the diazepine is H, whereas the reference teaches a $-CH_3$ at the 4-position of the diazepine ring. The reference's examples 6t, 6u and 6v, differ from the claimed invention only in the nature of the substituent on the 4-position of the diazepine ring system, i.e. H vs. Me. Hydrogen substituted diazepines are not patentably distinct from the methyl substituted diazepines in the prior art since the only difference is H vs. Me. H vs. Me is not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548 regarding the addition of a methyl group to a known compound. Furthermore, applicants should note a replacement of two methyl groups on a known compound with two hydrogen atoms has been held to be prima facie obvious due to close structural similarity. Note In re Hoke, 195 USPQ 148 and Ex parte Fauque, 121 USPQ 425. Thus, one having ordinary skill in the art would have been motivated to prepare the instantly claimed invention because such structurally homologous compounds are expected to possess similar properties.

5. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over SATO et al., EP 806 419. The prior art generically teaches compounds that are

structural homologs of the instantly claimed compounds as claimed herein, i.e., they differ by a methyl group. The instant compounds are structural homologs of the reference compounds where on the instant compounds the substituent at the 4-position of the diazepine is H, whereas the reference teaches a $-CH_3$ at the 4-position of the diazepine ring. The reference's examples in lines 19, 20, 21 and 23, differ from the claimed invention only in the nature of the substituent on the 4-position of the diazepine ring system, i.e. H vs. Me. Hydrogen substituted diazepines are not patentably distinct from the methyl substituted diazepines in the prior art since the only difference is H vs. Me. H vs. Me is not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548 regarding the addition of a methyl group to a known compound. Furthermore, applicants should note a replacement of two methyl groups on a known compound with two hydrogen atoms has been held to be prima facie obvious due to close structural similarity. Note In re Hoke, 195 USPQ 148 and Ex parte Fauque, 121 USPQ 425. Thus, one having ordinary skill in the art would have been motivated to prepare the instantly claimed invention because such structurally homologous compounds are expected to possess similar properties.

Claim Objections

6. Claim 14 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to the claims from which they depend in the alternative. See MPEP § 608.01(n).

37 CFR 1.75. Claim(s).

(c) one or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application. **Any dependent claim, which refers to more than one other claim (multiple dependent claim) shall**

refer to such other claims in the alternative only. A multiple dependent claim shall not serve as a basis for any other multiple dependent claims. For fee calculation purposes under § 1.16, a multiple dependent claim will be considered to be that number of claims to which direct reference is made therein. For fee calculation purposes, also, any claim depending from a multiple dependent claim will be considered to be that number of claims to which direct reference is made in that multiple dependent claim. In addition to the other filing fees, any original application, which is filed with, or is amended to include, multiple dependent claims must have paid therein the fee set forth in § 1.16(d). Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of each of the particular claims in relation to which it is being considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 703-305-1880. The examiner can normally be reached on 8:30-5:00 Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner Art Unit 1624
July 29, 2003